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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/823,447	04/13/2004	Scott Phillip Baron	PC20557A	4965

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WARNER-LAMBERT COMPANY
2800 PLYMOUTH RD
ANN ARBOR, MI 48105

EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/823,447	BARON ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-43* is/are pending in the application.

4a) Of the above claim(s) *1-9,11-13 and 15-40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14 and 41-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *13 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9-28-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election with traverse of group III, claim 14, in the reply filed on 10-4-06 is acknowledged. The traversal is on the ground(s) that claim 14 has been amended to recite the limitation of claim 10, therefore, groups II and III should be included in the same group. Applicants further argue that many of the standing 40 claims are classified in the same class and some of the claims are even classified in the same subclass, and there is no serious burden to search all the groups. This is not found persuasive because it is understood that claim 14 includes the nucleic acid molecules recited in claim 10. Since the sequence of SEQ ID No. 18 encompasses SEQ ID No. 17 and SEQ ID No. 19 encompass SEQ ID No. 18, SEQ ID Nos. 17-24 will be considered. Groups II and III are patentably distinct from each other because they are drawn to compositions having different chemical structures, physical properties, and biological functions: genetically-modified non-human mammal vs. nucleic acid molecules. They have different classifications and require separate search. Thus, groups II and III are patentably distinct from each other. Although both groups I and III have class 800 subclass 14, they are drawn to different genetically-modified non-human mammal comprising different nucleotide sequence encoding different protein that has different mutations. They are different mammals having different genotypes and phenotypes, and require separate search. Although groups IX-XI have same class 800 and subclass 3, they are distinct from each other because they are drawn to materially different methods that differ at least in objectives, method steps, reagents used, dosages and schedules used, response variables, and criteria of success. The rest of the groups are drawn to different classifications, i.e. different class and subclass. They are drawn to distinct

invention that require separate search, and there would be serious burden for examiner to search all the groups for the reasons or record.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-9, 11-13 and 15-40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 10-4-06.

Applicants' amendment filed 10-4-06 has been entered. Claim 10 has been canceled. Claim 14 has been amended. Claims 41-43 have been added. Claims 1-9 and 11-43 are pending. Claims 14 and 41-43 are under consideration.

Specification

3. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet **within the range of 50 to 150 words**. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract filed 4-13-04 only has 17 words. It is noted that the abstract should be in narrative form and generally limited to a single paragraph on a separate sheet **within the range of 50 to 150 words**. Appropriate correction is required.

Priority

4. If applicant desires to claim the benefit of a prior-filed application under 35 U.S.C. 119(e), a specific reference to the prior-filed application in compliance with 37 CFR 1.78(a) must be **included in the first sentence(s) of the specification following the title or in an application data sheet.** For benefit claims under 35 U.S.C. 120, 121 or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of the applications.

If the instant application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR

1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

Claim Rejections - 35 USC § 101

5. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 14 and 41-43 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

Claims 14 and 41-43 are directed to a genetically-modified non-human mammal comprising the nucleic acid molecule encoding the polypeptide sequence of SEQ ID No. 17, 18 or 19, and a genetically-modified non-human mammal comprising the nucleic acid sequence of SEQ ID No. 20, 21 or 22, or 23 or 24.

The specification discloses amino acid sequence of SEQ ID No. 17, encoded by exon 8 of mouse alpha2/delta1 subunit of voltage sensitive calcium channel with R217A mutation, amino acid sequence of SEQ ID No. 18, encoded by exons 8 and 9 of mouse alpha2/delta1 gene with R217A mutation, amino acid sequence of SEQ ID No. 19, encoded by exons 8-10 of mouse alpha2/delta1 gene with R217A mutation, and nucleotide sequences encoding the sequence of SEQ ID Nos. 17-19, i.e. SEQ ID Nos. 20-24 (see specification, p. 48-49). The specification demonstrate generation of a knockin transgenic mouse overexpressing R217A alpha2/delta1 mutant protein under the control of endogenous alpha2/delta1 promoter via homologous recombination in mouse ES cells and knocking in the R217A mutation in exon 8 (Example 1). The R217A mutant mouse shows reduced gabapentin binding to brain membranes as compared to wild type mice, and reduced efficacy of pregabalin in R217A mutant mice as compared to wild type or heterozygous mice (e.g. p. 38, 39). Pregabalin and Diazepam do not produce a significant anxiolytic-like effect in R217A knockin mice (e.g. p. 47). The specification asserts that the claimed genetically-modified, non-human mammal can be used for further defining the physiological role of alpha2/delta1 action, mechanism of action of alpha2/delta1 ligands in vivo,

and testing the role of alpha2/delta1 is disease process, such as anxiety, depression, schizophrenia, and bipolar disease etc. (e.g. p. 2).

The claimed non-human mammals encompass transgenic or chimeric non-human mammal comprising only the nucleotide sequence of exon 8, exons 8 and 9, or exons 8, 9 and 10 (each with R217A mutation) of the mouse alpha2/delta1 gene, or comprising nucleotide sequence encoding only the polypeptide sequence encoded by exon 8, exons 8 and 9, or exons 8-10 (each with R217A mutation) of the mouse alpha2/delta1 gene. However, the transgenic knockin mouse disclosed in the specification overexpresses the whole alpha2/delta1 protein with R217A mutation rather than a partial alpha2/delta1 protein sequence. The asserted utility for the claimed non-human mammals does not appears to be specific and substantial because the evidence of record has not provided any suggestion of a correlation between any phenotype of the claimed non-human mammals and a disease or a disorder. In fact, no phenotype has been disclosed for the claimed non-human mammals. The asserted utility of the claimed non-human mammal does not appear to be specific and substantial because no phenotype has been disclosed for the claimed non-human mammal and no correlation between a phenotype, if any, and a particular disease or disorder has been established. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the non-human mammal embraced by the claims. Therefore, the utility for further defining the physiological role of alpha2/delta1 action, mechanism of action of alpha2/delta1 ligands in vivo, and testing the role of alpha2/delta1 is disease process, such as anxiety, depression, schizophrenia, and bipolar disease etc., is not apparent.

The specification fails to disclose any phenotype of the claimed non-human mammal. A non-human mammal having no phenotype is indistinguishable from a wild-type non-human mammal and does not have a specific and substantial utility or a well-established utility because one skilled in the art would not know where and what to look for in using said non-human mammal. A substantial utility is a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. Absent the phenotype of the claimed non-human mammal and the correlation between a phenotype of the claimed non-human mammal and a particular disease or disorder, no "real world" use of the claimed non-human mammal has been established. Therefore, the claimed non-human mammal lacks a specific and substantial or a well-established utility.

In light of the above, the skilled artisan would not find the utility of the non-human mammal encompassed by the claims to be specific and substantial or well established.

Claims 14 and 41-43 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 14 and 41-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims read on numerous transgenic and chimeric non-human mammals, such as mice, rats, rabbits, sheep, pigs, canine, feline, monkeys, baboons, chimpanzees, whales, other mammals etc., expressing a partial alpha2/delta1 protein sequence and having a R217A mutation. The claims encompass numerous transgenic and chimeric non-human mammals having various unknown and unidentified phenotypes or having no phenotype. The specification fails to disclose any phenotype of the claimed non-human mammals. The phenotypes of the various claimed transgenic and chimeric non-human mammals were unpredictable at the time of the invention as discussed below. The structural features and phenotypes of the transgenic and chimeric non-human mammals that can distinguish said transgenic and chimeric non-human mammal from corresponding wild-type mammal have not been disclosed. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe common attributes or characteristics that identify the claimed transgenic and chimeric non-human mammals, and because the claimed transgenic and chimeric non-human mammals are highly variant, the disclosure in the present application is insufficient to describe the claimed transgenic and chimeric non-human mammals.

This limited information is not sufficient to reasonably convey to one skilled in the art that applicants were in possession of the claimed transgenic and chimeric non-human mammals. Thus, it is concluded that the written description requirement is not satisfied for the transgenic and chimeric non-human mammals.

10. Claims 14 and 41-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 14 and 41-43 are directed to a genetically-modified non-human mammal comprising the nucleic acid molecule encoding the polypeptide sequence of SEQ ID No. 17, 18 or 19, and a genetically-modified non-human mammal comprising the nucleic acid sequence of SEQ ID No. 20, 21 or 22, or 23 or 24.

The specification discloses amino acid sequence of SEQ ID No. 17, encoded by exon 8 of mouse alpha2/delta1 subunit of voltage sensitive calcium channel with R217A mutation, amino acid sequence of SEQ ID No. 18, encoded by exons 8 and 9 of mouse alpha2/delta1 gene with R217A mutation, amino acid sequence of SEQ ID No. 19, encoded by exons 8-10 of mouse alpha2/delta1 gene with R217A mutation, and nucleotide sequences encoding the sequence of SEQ ID Nos. 17-19, i.e. SEQ ID Nos. 20-24 (see specification, p. 48-49). The specification demonstrate generation of a knockin transgenic mouse overexpressing R217A alpha2/delta1 mutant protein under the control of endogenous alpha2/delta1 promoter via homologous recombination in mouse ES cells and knocking in the R217A mutation in exon 8 (Example 1).

The R217A mutant mouse shows reduced gabapentin binding to brain membranes as compared to wild type mice, and reduced efficacy of pregabalin in R217A mutant mice as compared to wild type or heterozygous mice (e.g. p. 38, 39). Pregabalin and Diazepam do not produce a significant anxiolytic-like effect in R217A knockin mice (e.g. p. 47).

The claimed non-human mammals encompass transgenic or chimeric non-human mammal comprising only the nucleotide sequence of exon 8, exons 8 and 9, or exons 8, 9 and 10 (each with R217A mutation) of the mouse alpha2/delta1 gene, or comprising nucleotide sequence encoding only the polypeptide sequence encoded by exon 8, exons 8 and 9, or exons 8-10 (each with R217A mutation) of the mouse alpha2/delta1 gene. However, the transgenic knockin mouse disclosed in the specification overexpresses the whole alpha2/delta1 protein with R217A mutation rather than a partial alpha2/delta1 protein sequence. The claims read on numerous transgenic and chimeric non-human mammals, such as mice, rats, rabbits, sheep, pigs, canine, feline, monkeys, baboons, chimpanzees, whales, other mammals etc., expressing a partial alpha2/delta1 protein sequence and having a R217A mutation. The claims encompass numerous transgenic and chimeric non-human mammals having various unknown and unidentified phenotypes or having no phenotype.

The specification fails to provide adequate guidance and evidence for how to make and use the claimed transgenic and chimeric non-human mammals. The specification also fails to disclose any phenotype of the claimed transgenic and chimeric non-human mammals. A transgenic and chimeric non-human mammal having no phenotype is indistinguishable from a wild-type mammal and one skilled in the art at the time of the invention would not know how to use the claimed transgenic and chimeric non-human mammals.

The level of one of ordinary skill in the art is high regarding making transgenic animal. The art of transgenics at the time of the invention held that the resulting phenotype of a transgenic animal was unpredictable at the time of the invention. Kappel et al., 1992 (Current Opinion in Biotechnology, Vol. 3, p. 548-553) reports that the individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct, the site of integration, etc., are the important factors that governs the expression of a transgene (e.g. p. 549)). Wall, R. J., 1996 (Theriogenology, Vol. 45, p. 45-68) states that "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior" (e.g. p. 61, last paragraph), and "transgene expression and the physiological consequences of transgene products in livestock are not always accurately predicted in transgenic mouse studies" (e.g. p. 62, first paragraph). Strojek et al., 1988 (Genetic Engineering: Principles and Methods, Vol. 10, pp. 221-246) points out that "genetic and species-specific conditions can cause different limitations or gene integration efficiency" and "transgenic mouse work alone is only of limited value when problems arising in the production of transgenic livestock are to solved, particularly when there is a necessity of finding cis-acting factors which are suitable for appropriate gene expression in a given species" (e.g. p. 238-239).

Further, the genetic background of the transgenic animal has a large impact on the resulting phenotype of the transgenic animals. Sigmund, C., June 2000 (Arterioscler. Thromb. Vasc. Biol., p. 1425-1429), reports that variation in the genetic background contributes to unpredictable resulting phenotypes of transgenic or gene-targeted animals. "Animals containing the same exact genetic manipulation exhibit profoundly different phenotypes when present on diverse genetic backgrounds, demonstrating that genes unrelated, per se, to the ones being

targeted can play a significant role in the observed phenotype" (e.g. abstract). Sigmund further states that "many of the phenotypes examined in transgenic and knockout models are influenced by the genetic background in which they are studies...Although all mouse strains contain the same collection of genes, it is allelic variation...and the interaction between allelic variants that influence a particular phenotype. These "epigenetic" effects can dramatically alter the observed phenotype and therefore can influence or alter the conclusions drawn from experiments" (e.g. introduction). Mogil et al., 1999 (Pain, Vol. 80, pages 67-82) reports that there are several limitations to the use of mouse transgenic KO models. Mogil teaches that "the embryonic stem (ES) cell lines used to carry the targeted mutation are all derived from various substrains of the 129 strain" and "it is difficult to separate by homologous recombination the 129-derived transgene from tightly linked gene. Even after repeated backcrosses to C57Bl/6, a step most often omitted in the competition to publish, the wild-type and KO populations will differ in their inheritance of so-called "hitchhiking donor gene" alleles". Knockout mutant mice will inherit alleles tightly linked with the gene disruption, leading to "hitchhiking donor gene" alleles from 129 ES cell lines while the wild-type mice will inherit C57BL/6-derived alleles. "[O]bserved phenotypic differences between wild-type and KO mice could, therefore, be due to the targeted mutation, to allelic variation at one or more of the many unidentified hitchhiking genes, or to an interaction between them" (page 78, left column). In addition, "the background genes from the parent strains can interact with the targeted mutation ("epistasis"), importantly affecting the observed phenotype" (page 78, left column).

In addition, Mercier et al., 1997 ("The modification of milk protein composition through transgenesis: progress and problems," In: Transgenic Animals: Generation and use, Ed.

Houdebine LM, Harwood Academic Publishers, The Netherlands pp: 473-482) teach that "much progress remains to be done before routinely using transgenesis for generating farm animals producing milk for non-therapeutic use. In the present state of the art, it is difficult to predict that a construct will be functional because of insufficient knowledge on gene transcript, Pre-mRNA processing, RNA and protein stability. Integration of the microinjected transgene is aleatory resulting in highly variable levels of expression, and possible detrimental effects." (e.g. p. 479, right column). It appears that the individual gene of interest, promoter used, enhancer, coding or non-coding sequences present in the transgene construct, the site of integration, and the genetic background of the transgenic animal determine the expression level of the desired gene product and the resulting phenotype of the transgenic animals.

The claims encompass using homologous recombination to produce transgenic non-human mammals. When using homologous recombination to produce a transgenic non-human mammal, embryonic stem cells are used for the homologous recombination. Houdebine, L-M., 2002 (Journal of Biotechnology, Vol. 98, p. 145-160) states that "animal transgenics is still suffering from technical limitations" (e.g. abstract). Gene replacement by homologous recombination in somatic mammalian cells has relatively poor efficiency and "For unknown reasons, homologous recombination is more frequent in pluripotent embryonic cells" (e.g. p. 148, right column). However, gene transfer or inactivation using embryonic cells has failed in species other than mouse, and "the recombined ES cells have more or less the capacity to participate to the development of chimeric embryos but that transmission of the mutation to progeny has been observed so far only in two mouse lines and essentially of the 129/SV line...The systematic lack of success met in rat, rabbit, chicken, pig, sheep and cow now inclines

to consider that the so- called ES cells cannot be used for the germinal transmission of a mutation except in two mouse lines systematic studies to tentatively identify genes involved in the two mouse lines are in course" (e.g. p. 149, left column). Thus, the use of embryonic stem cells to make transgenic non-human mammals via homologous recombination at the time of the invention was not enabled other than the two mouse lines in view of Houdebine.

A partial protein sequence could have dramatically different biological function from a complete protein sequence. It was known in the art that the amino acid sequence of a polypeptide determines its structural and functional properties (including half-life), and predictability of which amino acid(s) can be removed from or added to a polypeptide's sequence and still result in similar activity or result in stabilization of the protein is extremely complex, and well outside the realm of routine experimentation. Rudinger, 1976 (Peptide Hormones, Parsons, University Park Press, Baltimore, p. 1-7) points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) discloses that a single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding (e.g. title). In addition, Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not

necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). Therefore, biological function of a protein or peptide was unpredictable from mere amino acid sequence at the time of the invention. The biological functions of the partial mouse alpha2/delta1 R217A protein sequences were unpredictable at the time of the invention and such unpredictability further contributes to the unpredictability of the resulting phenotype of the claimed transgenic non-human mammals.

The claims also read on chimeric non-human mammals expressing a partial alpha2/delta1 protein sequence and having a R217A mutation. The specification fails to enable making chimeric non-human mammals expressing a partial alpha2/delta1 protein sequence and having a R217A mutation, and no phenotype of the chimeric non-human mammals has been disclosed. The specification does not correlate chimeric non-human mammal to any phenotype. The method of making genetic mosaic animal is such that each resulting chimera is comprised of a different, unpredictable ratio of cells of various genotypes. This ratio cannot be predetermined. Furthermore, the spatial distribution of cells of each genotype cannot be predetermined. Therefore, the phenotype of chimeric animal is not only dependent upon the genotype of the cells (which is unpredictable as set forth by the state of the art outlined above, for example see Mogiol; Sigmund) but is also dependent upon the spatial distribution of the cells and their relative population size. Thus, the phenotype of the chimeric non-human mammal encompassed by the claims is highly unpredictable. The specification fails to provide the guidance necessary to overcome this high level of unpredictability to generate a chimeric non-human mammals exhibiting any specific phenotype or any phenotype other than wild type. As set forth above,

without a predictable phenotype, it would require additional and undue experimentation for one of skill in the art at the time of the invention to determine the phenotype of a chimeric non-human mammal and how to use said chimeric non-human mammal.

In view of the unpredictable biological function of a protein or peptide, the inherent unpredictability of the resulting phenotypes of transgenic animals and chimeric animals, the limitation of the embryonic stem cells that can be used to make transgenic animals, and the lack of any phenotype of the claimed transgenic and chimeric non-human mammals, one skilled in the art at the time of the invention would not know how to use the claimed transgenic and chimeric non-human mammals. For the reasons set forth above, one skilled in the art at the time of the invention would have to engage in undue experimentation to practice over the full scope of the invention claimed. This is particularly true based upon the nature of the claimed invention, the state of the art, the unpredictability found in the art, the teaching and working examples provided, the level of one of ordinary skill which is high, the amount of experimentation required, and the breadth of the claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER